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PRINCIPAL INVESTIGATOR: Lee Josephson, Ph.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

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Lee Josephson, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Massachusetts General Hospital
Boston, MA 02114

E-Mail: josephso@helix.mgh.harvard.edu

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An MR contrast agent targeted to the GRP receptor will be a novel pharmaceutical capable of non-invasively, and at high spatial resolution, characterizing healthy and pathological regions within the prostate. The goal of the research is to develop a magnetic nanoparticle MR contrast targeted to the gastrin releasing peptide receptor (GRP receptor) that will be used to image the intra-prostatic distribution of this key molecular marker. Because of technical problems in imaging the GRP receptor in animal models of prostate cancer, we have been imaging the expression of this receptor in the normal mouse pancreas. Our long term goal is to use this animal model to refine our understanding of the interaction of magnetic nanoparticles with this receptor and return to the animal prostate cancer models.

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Introduction

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Results and Discussion (Body)

The third year of our work plan was initiated and will be completed in the extension of time requested. The original goal was to image the expression of the GRP receptor using in an animal model of prostate cancer. We have initiated imaging studies with the bombesin peptide-nanoparticle conjugate developed during years 1 and 2 of the current research by imaging the receptor in a convenient animal model, the normal mouse. The GRP receptor is expressed at high levels in the normal rodent pancreas.

I. Synthesis of peptide-nanoparticle conjugates

Based on earlier studies optimizing the peptide and peptide nanoparticle, we have use the bombesin-like peptide below in the current studies along with succinimidyl acetic acid as a conjugating reagent. Bombesin-like peptide = FITC-bACdddGQRLGNQTAVGHLM, where b= beta alanine.

II. Preliminary studies imaging the of GRP receptor in normal mouse pancreas by fluorescence reflectance imaging.

We have employed fluorescence reflectance of imaging of dissected tissues to examine the specificity of our BN-CLIO(Cy5.5) nanoparticle as shown in Figure 1. Animals were co-injected with BN-CLIO(Cy5.5) and scramBN-CLIO(Cy3.5), a nanoparticle made with a scrambled peptide. The Cy5.5 fluorescence above the intrinsic fluorescence of the pancreas (about 100 AU) indicated the nanoparticle was accumulated due to the presence of the BN peptide, which is a demonstration that the nanoparticle is inacting with a receptor, the GRP receptor, which binds this peptide.

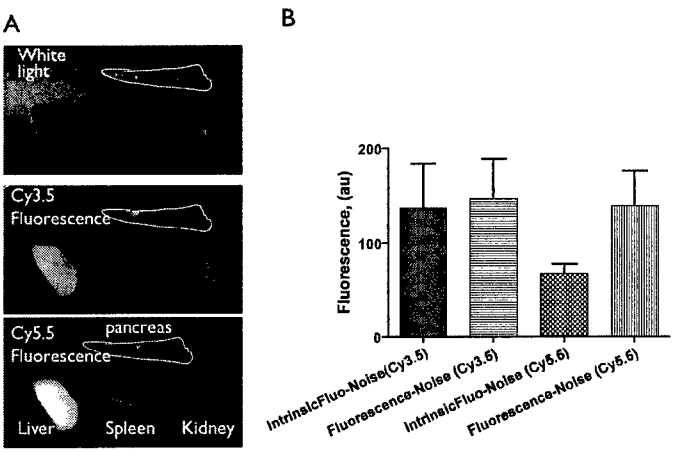

Figure 1: Fluorescence reflectance imaging of dissected mouse tissues. (A) White light and fluorescence images of dissected tissues. (B) Analysis of pancreatic fluorescence. Cy5.5 but not Cy3.5 fluorescence increased over background.

III, Preliminary studies imaging the GRP receptor in normal mouse pancreas by MRI.

We have begun MRI imaging with our BN-CLIO(Cy5.5) nanoparticle as shown in Figure 2. Animals were injected with BN-CLIO(Cy5.5) or CLIO at 10 mg Fe/kg and imaged 24 hours later. BN-CLIO(Cy5.5) produces a darkening of the mouse pancreas that was greater than the control nanoparticle that did have BN peptide (CLIO nanoparticle).

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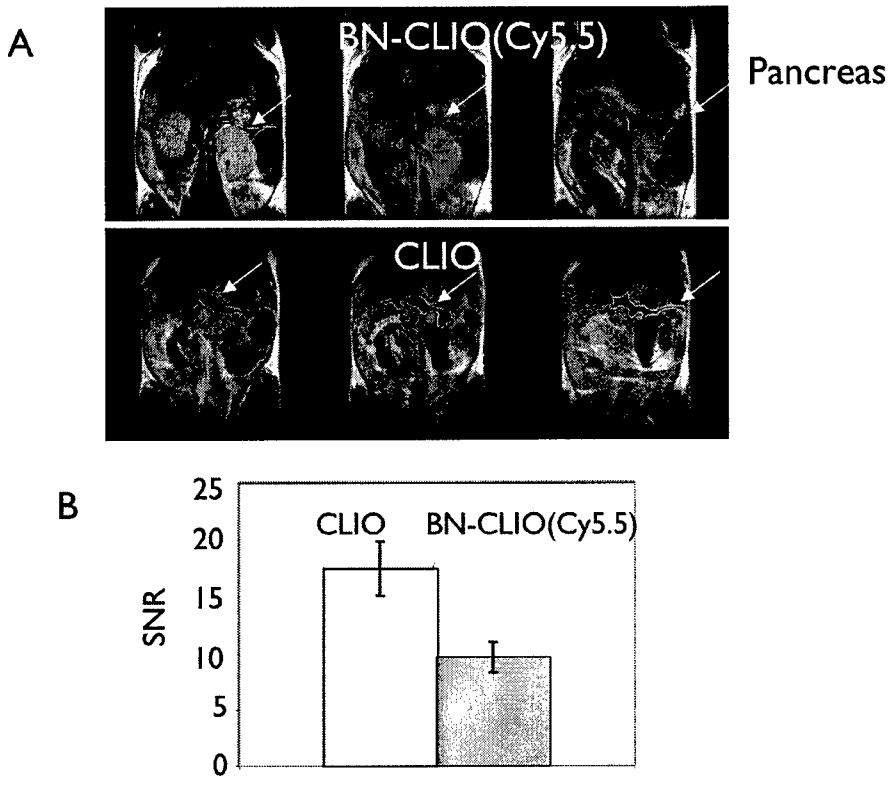

Figure 2: MRI of mouse pancreas after injection of BN-CLIO(Cy5.5) or CLIO nanoparticle. (A) MRI images of three planes of a mouse injected with nanoparticles (B) Decrease in signal produced by BN-CLIO(Cy5.5) or CLIO in the pancreas. BN-CLIO(Cy5.5) causes a bigger change in fluorescence.

Key Research accomplishments

- We have obtained encouraging data that the BN-CLIO(Cy5.5) is targeting the GRP receptor by fluorescence reflectance imaging. However, greater numbers of animals are needed to insure significance of this result.

- We have obtained encouraging data that the BN-CLIO(Cy5.5) is targeting the GRP receptor by MRI However, greater numbers of animals are needed to insure significance of this result.

Conclusions

- Preliminary experiments using the mouse pancreas as a organ bearing the GRP receptor suggest but do not prove that the BN-CLIO(Cy5.5) nanoparticle is targeting the GRP receptor and that it can image this receptor. Further experiments are justified and needed to substantiate these results.

Reportable Outcomes

- The mouse pancreas can be used to image the interaction of nanoparticles with the GRP receptor. This avoids the need to generate tumor models to design and study the interaction of the nanoparticle in an animal model.

- The BN-CLIO(Cy5.5) nanoparticle can be detected by fluorescence reflectance imaging or MRI in the normal pancreas after IV injection at 10 mg Fe/kg.